ammonia ratio, is normal, whereas often in chronic nephritis there is a definite inability to utilize ammonia.[7]

The fact that a severe acidosis is present, that the acid ammonia ratio is normal, and that nevertheless the total NH_3 excretion is not increased shows very clearly that the excretion of acid is greatly impaired.

The clinical picture is similar to that commonly found in bilateral cystic disease of the kidneys. Pain and digestive symptoms are common at the onset. Edema is rare. Terminal uremia is usual. The urine is usually increased in amount, with little or no albumin, low gravity, and no casts. The blood-pressure often shows no elevation.

THE INVASIVE QUALITY OF THE STREPTOCOCCI IN THE LIVING ANIMAL.[1]

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Invasion, virulence, and pathogenicity as well as resistance and susceptibility are all relative terms and must be considered from the point of view of the animal body as well as the bacteria themselves. This is generally recognized but is not constantly remembered.

The streptococci have primarily high invasive powers. By this I mean that they are capable of entering the animal body under a wide variety of conditions. It is only within the last few years that this has been broadly recognized. The Bacillus coli formerly was the organism found as the chief secondary invader. In autopsy bacteriology the colon bacillus is frequently reported as the common bacterium invading after death, and in studies of peritoneal and other fluids the same organism was found practically to the exclusion of all others. More careful technic has, however, definitely shown that streptococci of various types invade the tissues and body fluids long before the colon bacillus, and are, moreover, almost always present where the latter is found. A long series of blood cultures taken by workers in our laboratories from the arm vein immediately or shortly after death, as well as numerous cases reported in the literature, serve to demonstrate this fact. Numerous investigators have further shown that this invasion by streptococci is more commonly antemortem and often occurs as the so-called agonal infection.

[7] Palmer and Henderson, loc. cit.

[1] Read before the American Association of Pathologists and Bacteriologists, Washington, May 10, 1916.

From these cases illustrating the invasive power of the streptococci under definite recognizable conditions of damaged resistance we are able to follow a graded series of cases in which invasion took place hours, weeks, months, and years before death as also innumerable examples when death did not result from the invasion. Many investigators believe that streptococci are frequently invading the body, but that under conditions of relatively good health they are being continually destroyed.

It is certainly true that streptococci invade the blood stream more often than most other bacteria. Their demonstration is not always easy, as they frequently only temporarily invade the blood. It is not uncommon to find that 10 c.c. of blood fails to reveal the organisms while 15 c.c., 20 c.c., or 25 c.c. may be required to demonstrate a siagle coloay. We are limited, for obvious reasons, in the amount of blood we can take, and therefore we endeavor to choose a time when the mmber of bacteria in the blood is greatest. There is no royal road to successful blood cultures in many of these cases. Serum broth with or without carbohydrates is probably the best medium and by adding a tube of melted agar, anaërobic cultures are readily made. In this as in many similar tests a positive result is important; a negative leaves the question open. There is ample evidence to show that streptococci found in various lesions of the body have probably been distributed by the blood stream, but the invasion from the nearest naturally infected parts of the body must always be first considered.

The portals of eatry for streptococci are wide-spread and do not play as important a role in the invasion as is the case with other bacterial groups. The organisms may enter the body from the mucous membranes of the throat, that of the intestinal tract, the uterus, from the skin, and many other points. Naturally, the conditions will vary soaiewhat according to the types of tissue encountered by the organisms. Whether they further increase in numbers and bring about damage depends largely upon the relative susceptibility or resistance of the different tissues of the body; that is, the environmental conditions they eacounter. I do not assume there is a specificity on the part of the streptococci as to what tissue or organ they attack, but, granted that the natural distribution plays no part, I am convinced that they locate in whatever areas offer the proper conditions of relative susceptibility. No two animals offer the same conditions for the invasion of bacteria nor identical susceptibility or resistance in all their tissues. It is true, no doubt, that a group of animals or human beings living under the same conditions will tend, more or less, to similar tissue susceptibilities, and that at different seasons of the year alterations in temperature and moisture of the air, changes in food and ventilation, and number of other environmental conditions will tend to alter these susceptibilities in the entire group.

Nevertheless, certain individual differences will still persist. Many experiments on animals demonstrate this variability in tissue susceptibility in different groups of the same race of animals. Everyone is familiar with family susceptibility as well as individual variations following the same infection. These facts are often forgotten when animals are used in the study of bacteria, but being remembered will often prevent misinterpretation of results.

By virulence of the streptococci I mean something further than invasive power. Virulence is the ability of bacteria to multiply in the tissues, to resist the defensive mechanism, to increase the susceptibility (probably by toxins) of the tissues, and to prepare the way for the manifestations of pathogenicity. If the virulence is high the incubation period is reduced and the pathogenic characters are seen early. It is relatively common in infections with hemolytic streptococci to have a slight local reaction at the portal of entry. The virulence in these cases is very intense and the resistance is rapidly overcome.

Three groups of streptococci have been arranged as follows: (1) Those lacking in invasive, virulent, and pathogenic qualities; these include the strictly saprophytic forms, which I believe are very rare. (2) Those with well-developed, slowly acting virulence (possibly on account of a similarity of metabolic activity to that of the host) but with definite and eventually, when the infection continues, severe pathogenic powers; in this group we have the Streptococcus viridans organisms. (3) Those with powerful invasive power, active virulence setting up violent defensive reactions and exhibiting a high pathogenicity. Under these we have the hemolytic streptococci.

There are a number of conditions that modify the demonstration of these qualities. The portal of entry may be more or less favorable to a rapid manifestation of all these characters. Locally, highly resistant tissues may check either the invasion, the further growth of the bacteria (virulence), or the pathogenicity, while other tissues offer more favorable conditions, particularly mucous membranes in which disease processes, set up by the invading organisms or other bacteria, may offer a ready entrance for the bacteria to underlying structures or the general circulation. The number of bacteria invading the body will also greatly influence the virulence and the pathogenicity. This is particularly to be remembered in consideration of invasion from primary infected foci such as are found in the tonsils, gums, intestinal tract, uterus, and other parts. These local foci also serve as points in which the bacteria may fully develop their invasive, virulent, and pathogenic characters. They serve, as it were, as training grounds for the bacteria. The increase in these qualities is within fairly narrow limits. The hemolytic streptococci, which are the strains capable of becoming highly virulent and pathogenic, may here not only increase in

numbers but develop more rapidly these qualities. The members of the Streptococcus viridans group may also have the opportunity in these foci of increasing in their characters, but only within the limits of the group, and at no time do they develop the type of virulence and pathogenicity found in the streptococcus hemolyticus group.

There is another condition found in these foci which has led to much confusion among early investigators, and that is the presence in them of a mixture of bacteria. Such foci develop as the result of a lowering of resistance in the local tissues and the invasion of bacteria of the grade of virulence proportionate to the condition. Following this several things may happen: the bacteria may increase in disease-producing power within their capabilities or they may prepare the way for more vigorous types of organisms, the two or more growing commensally or until the weaker succumbs. At any time during this process a further invasion of tissue or the blood stream may occur by the original organisms, the mixture, the dominant organisms in the mixture, or by the surviving strains. In any case the organisms invading the body will either be overcome or will cause secondary foci in those tissues in which the environment resulting from the noxious influence of manifold agencies including toxins is favorable for their development.

These possibilities which I have cited are what actually occur. We find infected foci with one type of streptococcus or with two or several types as well as with other bacteria. We can frequently demonstrate the entrance of a new type and its survival in various stages of the process. When the blood stream is invaded it is most commonly by one organism, but by no means infrequently by two. This blood stream invasion is mostly transitory, but sufficient to give rise to secondary foci from which corresponding types of organisms may be recovered. Furthermore, these secondary foci may serve as new distributing points. Wrong interpretations of these findings have led to most astonishing "biological alterations and mutations."

What appears to be the obvious focus of infection is not always the source from which invasion actually occurs. An inflammatory process of the intestinal tract synchronous with pyorrhea, for example, may be the condition leading to the invasion of bacteria. It is, indeed, often extremely difficult to be certain of the conditions present, and we should be very careful in drawing dogmatic conclusions from our necessarily limited findings.

There are certain states of lowered resistance that appear to be favorable for the invasion and activity of one or other of the two main streptococcus groups. In the puerperal state and in scarlet fever the conditions usually favor an infection by the hemolytic streptococci while chronic irritations, such as are found in the stomach, kidneys, and other organs from a variety of causes,

general lack of tone following sedentary life, exposure to cold and dampness, and many other similar, often temporary, lowerings of resistance offer conditions most suited to the attack of the non-hemolytic streptococci. In perforations of the intestinal tract in which the non-hemolytic strains are numerically greatly in excess of the hemolytic, judging from cultures of the intestinal contents, it is usually the latter which survive and cause the severe results, which means that the hemolytic forms can withstand the active defenses of the body better than the non-hemolytic; in other words, they are more virulent.

The members of the hemolytic streptococcus group include the strains with the highest virulence and pathogenicity. They are the causative agents in the most severe types of streptococcal disease, such as severe septicæmia, erysipelas, peritonitis, and other pyogenic infections. These infections give severe local or general reactions and are often fatal, but even with recovery we have the clinical picture of severe acute disease.

The streptococci of the viridans group, on the other hand, are the common cause of chronic infections. They have high invasive power and attack tissues in a state of lowered resistance, stimulate little reaction on the part of the body, apparently render the tissues more susceptible to reinfections, and death, if it occurs, only follows after a prolonged course or repeated reinfections. Clinically these cases are characterized by a relatively mild and chronic course with frequent exacerbations. Occasionally a Streptococcus viridans strain prepares the way for a hemolytic strain and the disease becomes a more severe one, and in cases recovering from a hemolytic streptococcus infection an invasion may occur with one of the non-hemolytic forms.

A proper classification is necessary to enable us to recognize the various varieties of streptococci. The method which I have been following for some time and which is published this year has enabled me to greatly enlarge my views on the invasive and other qualities of the streptococci. I have been able to recognize mixtures of different streptococci belonging to both of the two main groups and to trace the source of the invasion in many cases. There is one important point which has been noted in this study, and that is that the streptococci are not specific in their disease production. There is no evidence to support the view that only one type of streptococcus produces endocarditis or nephritis or gives rise to septicæmia in the puerperium, scarlet fever, or other conditions of lower resistance. Neither do I believe that one streptococcus is responsible for all the ill effects in all of these cases. Streptococci of several kinds live in symbiosis in the mouth and the intestinal tract. They are often found in mixtures in other infected areas as in the peritoneal, pleural, and other cavities. The blood stream may be invaded by more than one type, although, as a rule, we only

recover one. It is, therefore, not surprising to find different organisms locating in various damaged areas. Under these conditions by the use of the hemolytic test alone we are liable to draw erroneous conclusions. Thus by this single method, without the carbohydrate fermentation tests, the various members of the viridans or hemolytic groups cannot be distinguished.

There are many interesting points for discussion in tracing the source of many of the streptococci. The streptococcic flora of the mouth has always been confusing. The finding of mouth streptococci in the air of rooms as shown by Gordon may be taken as indicating pollution of the air from the oral cavity and thus the flora of the mouth is continually being replenished from the mouths of others. Another source of origin for these streptococci appears to be cows' milk which in turn is subject to contamination from the cows' feces while still a third source is the air streptococcus derived from horse manure. In the mouth cavity many of these strains find favorable conditions for further development. Broadhurst has shown that many streptococci, being swallowed in the sputum, can pass through the stomach without being destroyed in the limited time by the gastric juices. In the intestinal tract the cultural conditions are markedly different from those of the mouth, and many of these strains are destroyed, while others, especially the more vigorous forms, such as Streptococcus fecalis and Streptococcus equinus, flourish and produce a flora quite different from that found in the mouth.

It cannot be too often repeated, however, that the entire flora of any region of the body may be suddenly changed by alterations in the food supplied to the bacteria, the reactions of the secretions, the presence of inflammation, and many other important environmental changes. Particular streptococci finding these new conditions favorable, multiply rapidly and the former inhabitants are crowded out. In diphtheria, for example, streptococci may greatly increase in numbers and seriously complicate the conditions, as has been repeatedly pointed out by Le Gros and others. Although the streptococci present in the greatest numbers in normal saliva and intestines are of the viridans group, a careful search will almost always reveal members of the hemolytic group, and these, as experience teaches, are the strains most capable of producing severe infections. In this connection the influx of strains from disease sources outside of the body, in which the streptococci have developed to a high degree, their disease-producing characters must not be forgotten.

It is beside the point to argue that streptococcus infection in rheumatism and other diseases is a secondary invasion. It is most certainly true that in practically all our infections the bacterial attack is secondary to the necessary conditions of lowered resistance. In many of these arguments one is reminded of Pettenkofer's

demonstration to prove that the cholera vibrio does not always cause epidemics of cholera.

The condition of lowered resistance in the Streptococcus viridans infections are receiving much attention but we are only on the threshold of this study. When the streptococci have established themselves within the system we are usually at a relatively late stage of the disease. Libman has shown that in viridans endocarditis the cases may become spontaneously bacteria-free. The work of many of the German workers would indicate, though on somewhat dubious grounds, that the viridans endocarditis is almost always eventually fatal. There is no doubt that with more careful blood cultures the frequency of viridans infection in the earliest stages is being shown and the recurrent attacks are being guarded against (Oille, Graham, and Detweiler).

Spontaneous streptococcus infections in animals is a frequent occurrence. I have isolated streptococci from about half of 200 guinea-pigs infected spontaneously. In most of these the streptococcus infection was the cause of death, but in others the streptococci were definitely secondary invaders during the course of other infections. In certain animals dying of a hemolytic streptococcus infection of the lungs, for example, non-hemolytic streptococci have been isolated from the peritoneal fluid. I have further demonstrated that streptococci found in the alimentary tract will invade the animal body following injections of dead or living colon bacilli as also after injecting various forms of streptococci. Numerous similar results have been recorded in the literature, but not uncommonly these have been misinterpreted.

It must not be forgotten that in injecting streptococci into animals we are overlooking some of the most important characters of these bacteria. Subcutaneous and intraperitoneal injections of large doses may serve as tests for the further invasive power of the bacteria from these sites, modified by the local injury resulting from the injections, while intravenous injection completely ignores the invasive character. The streptococci by this latter method, finding themselves in the circulation, naturally locate in various organs, and, according to the grade of virulence, will multiply in those tissues in which the susceptibility is of the corresponding grade. The irritation, both mechanical and that arising from the products of growth in the vehicle, will frequently bring about local reactions, which may or may not favor the development of virulence. Infiltration of the tissues with polymorphonuclear leukocytes will frequently follow large injections while only mononuclear response may result from small doses.

Streptococci derived from sources in which the natural infection did not result in a polymorphonuclear reaction may give rise, when injected in large doses, to such n reaction. It is therefore not to be concluded from the unnatural conditions of such experi-

ments that the response elicited is fundamentally characteristic of the bacteria. The study of natural infection demonstrates that the two main groups of streptococci call forth quite different responses, and animal experiments would be of value if we could determine the minimal dose which calls forth any reaction, as this would more nearly approach the natural condition. The products of growth of the bacteria, be they toxins or other excretions, probably determine the character of the response in susceptible tissues, and these two groups differ in the type of reaction they stimulate, the hemolytic streptococci calling forth more active responses and the non-hemolytic a slower and more chronic type of reaction. If we use the same dose of one streptococcus with a certain virulence and find the same tissues affected in the majority of the injected animals it will serve as a test to indicate the susceptibility of these tissues in the particular group of animals. Even varying doses may at times demonstrate the same thing. Further, this same streptococcus having had its virulence raised will attack other tissues which were resistant in the previous experiments. All these and many other points serve to emphasize the importance of the relations existing between the host and the infecting organism.

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